A STUDY ON

CARDIAC AUTONOMIC NEUROPATHY

IN RHEUMATOID ARTHRITIS

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MADURAI MEDICAL COLLEGE, MADURAI

CERTIFICATE

This is to certify that this dissertation titled "**A STUDY ON CARDIAC AUTONOMIC NEUROPATHY IN RHEUMATOID ARTHRITIS** submitted by **DR.K.SHAJUDEEN** to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

DR. C.DHARMARAJ MD., DCH
Professor of Medicine,
Chief, VII Medical Unit,
Department of Medicine,
Madurai Medical College,
Madurai.

DR.MOSES K DANIEL M.D.,
Professor and HOD
Department of Medicine,
Madurai Medical College,
Madurai

DECLARATION

I**, DR.K.SHAJUDEEN ,** solemnly declare that the dissertation titled "**A STUDY ON CARDIAC AUTONOMIC NEUROPATHY IN RHEUMATOID ARTHRITIS"** has been prepared by me. This is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the regulations for the award of MD degree (Branch I) General Medicine.

Place: Madurai

Date: **DR.K.SHAJUDEEN**

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CONTENTS

S NO.	CONTENTS	PAGE NO
1.	INTRODUCTION	1
2.	REVIEW OF LITERATURE	2
3.	AIMS AND OBJECTIVES	37
4.	MATERIALS AND METHODS	38
5.	RESULTS AND ANALYSIS	49
6.	DISCUSSION	59
7.	SUMMARY	66
8.	CONCLUSION	68

APPENDIX

BIBLIOGRAPHY

PROFORMA

MASTER CHART

ETHICAL COMMITTEE APPROVAL FORM

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multisystem disease of autoimmune aetiology. The characteristic feature is the persistent inflammatory synovitis usually involving peripheral joints in a symmetric distribution. Though it is considered a disease predominantly involving the joints it can cause a variety of extra articular manifestations. It can affect skin, eye, cardiovascular, respiratory and nervous systems and may produce haematological complications including an increase in the risk of Hodgkin's disease, non Hodgkin's lymphomas, leukemias independent of the immunosuppressive drugs. One of the important extra articular manifestations is the involvement of nervous system. Neurological manifestations may be due to the involvement of central nervous system, peripheral nervous system or autonomic nervous system. They may be either due to the vascular involvement, direct compression or immune mediated mechanism. Autonomic neuropathy in Rheumatoid arthritis is rare. But recent studies have shown variable results and it varied from 0-70% symptomatic or asymptomatic. It can effect parasympathetic only or sympathetic only or both. Most common is the parasympathetic involvement. An important adverse effect of autonomic neuropathy is

cardiac autonomic neuropathy, as it can lead to increase in morbidity and mortality. Cardiac autonomic neuropathy can lead to sudden cardiac death, various arrhythmias, adverse effect to drugs, increase incidence of frequent falls especially in elderly further aggravating the morbidity.

REVIEW OF LITERATURE

Epidemiology

RA is widely distributed all over the world and affects all races. The prevalence in the adult population is assessed at approximately 0.5 to 1.The prevalence and incidence is 3 times higher in the females than the males[2]. The incidence of RA rises dramatically during adulthood. The average age at onset has shifted upward over the past five decades. There is a decline in the age specific incidence and is greatest in females [1].

Aetiopathogenesis

The genetic predisposition and the environmental factors(importantly infections) play a major role in the causation of RA. The HLA class II molecule particularly HLA DR4 is associated with 70% of RA patients. The susceptibility to RA is associated with the third hypervariable region of the DR β chains from amino acids 70 through 74 [3]. Deficient galactosylation of the immunoglobulin G might also be a risk factor for the development of RA. Association with genetic polymorphisms have been demonstrated with tumour necrosis factor–alpha, chemokines and other cytokines. A single nucleotide polymorphism for the T-cell co-stimulatory molecule CTLA 4 is

also associated with susceptibility. Infectious agents play an aetiologic role in the causation of RA. The bacterial organisms are pathogenic through molecular mimicry and viruses cause direct synovial infection or induce polyclonal activation as in Ebstein-Barr viral infection.

Rheumatoid factor was the first evidence of autoimmunity in RA. Rheumatoid factor (RF) is an autoantibody against the antigenic determinant region in the Fc portion of the IgG molecule. The IgG becomes immunogenic through various mechanisms. First, new determinants on IgG might be exposed after polymerization of molecules or formation of IgG complexes with specific antigens. Second structural anomalies in the IgG of the RA patients may render it immunogenic. Finally changes in the relative extent of the galactosylation of the IgG may give rise to auto antigenic reactivity[4]. Production of high affinity RF leads to intra articular complement fixation and synovitis. High titer IgG RF is associated with vasculitis, IgA RF is associated with erosions and vasculitis. Apart from that autoantibodies directed against the components of the articular cartilage like type II collagen, gp39, cartilage link protein, proteoglycans and aggrecans and nonarticular antigens like citrullinated peptides, glucose 6-phosphoisomerase, HLA–DR, heatshock proteins, hnRNPA2 also play a

vital role in the pathogenesis of RA. Patients with active rheumatoid disease may develop encephalopathy, myelopathy, peripheral neuropathy, autonomic neuropathy and myopathy through a variety of tissue mechanisms. Brain involvement is usually characterized by the formation of rheumatoid nodules or by the development of vasculitis or its complications, and there is evidence to suggest that the trapping of immune complexes within the choroid plexus may be important in pathogenesis.

Structural damage to the spinal cord and lower brain stem, on the other hand, most commonly results from narrowing of the bony canal, leading either to direct compression of neural tissue or to compromise of its vascular supply or due to atlanto axial subluxation following the loss of support from the transverse, alar and apical ligaments due the inflammation at the synovial bursa which is present in between the transverse ligament and the odontoid process. The appearance of peripheral neuropathy generally signifies the presence either of inflammatory epineurial arterial disease or entrapment by neighbouring anatomical structures. Skeletal muscle dysfunction may be due to vasculitis, myositis, or denervation atrophy. Both systemic and local anatomical factors, therefore are of importance in determining the manner in which different parts of the nervous system may

be affected in rheumatoid disease. Serum levels of soluble VCAM-1, soluble E-selectin, and Anti Endothelial Cell antibody are higher in patients with RA neuropathy than in patients with RA uncomplicated by neurological disease. These data suggest that development of peripheral neuropathy in RA is associated with increased endothelial cell activation[5]

Autonomic neropathy in rheumatoid arthritis may be either due to the vascular involvement, direct compression or immune mediated mechanism. s.maule,r.quadri,d.mirante et al has found that an association between the complement fixing autoantibodies directed against the sympathetic ganglia and vagus nerve and asymptomatic autonomic dysfunction. This auto antibodies occurred independenly of the presence of other conventional autoantibodies,thus indicating that their target antigens are tissue specific. The nature of these antigen remains to be determined.[6]

Pathology

The primary site of immune activation in RA is the synovium of the joint. Infiltration of synovium with mononuclear cells, especially T cells and macrophages, and synovial intimal lining hyperplasia are the hallmarks of the disease. The increase in the synovial intimal lining cells is substantial. The two types of synoviocytes, type A and B are increased in RA with the

predominance of type A macrophage like cells which express the markers CD 68,Fc receptors,CD14 and abundant HLA –DR molecule. In chronic RA the synovium contains a collection of T lymphocytes that can lead to an organizational structure resembling a lymphnode. These collections consist of small CD4+ memory cells. T cells constitute about 50 % or more of cells in most RA synovia, and most are CD4+, only 5% or fewer of cells are B lymphocytes or plasma cells. Oligoclonal expansion of CD4+ CD28- T cells are poor B cell stimulators and occur more frequently in patients with extra articular manifestation. Synovial lymphocytes also bear adhesion molecules of very late antigen and lymphocyte function associated antigen super family of integrins, which may enable the inflammatory process to persist within the synovium. The cytokine milieu of the synovium induces the expression of ICAM-1, VCAM-1 and connecting segment -1 fibronectin on vascular endothelium. Chemokines and the chemokine receptor especially CCR5 play a vital role in the accumulation of T cells independent of a particular antigen. Synovial B cells and plasma cell hyperactivity take part in the perpetuation and initiation phase of RA. Dendritic cells constitute around 5% of synovial cells which has resistance to the effects of IL-10.Other cells present in the synovium are polymorphonuclear cells, mast cells. Synovial tissue express Th1 cytokine bias which comprises IFN-γ, IL-2 and IL-

17.Macrophages are the major source of cytokine secretion in the synovium. Activation of macrophages and fibroblasts occur also through cell to cell contact with T-lymphocytes. The pro inflammatory cytokines IL-1,IL-6,TNF-alpha,IL-15,colony stimulating factors, chemokines, platelet derived growth factor and fibroblast growth factor all play an important role in the establishment of the synovial pathology. Underproduction of suppressive cytokines like IL-1Ra ,IL-10,TGF-β and soluble cytokine receptors and binding proteins may also contribute for the synovial inflammation. The most important mechanism of the bone and cartilage destruction is the pannus formation which is a cellular layer. Aggressive degradation of the extracellular matrix occurs at the pannus cartilage junction. The enzymes induced by the factors IL-1, TNF-alpha, phagocytosis of debris by synovial cells and mechanic trauma cause the joint destruction. The MMP s and aggrecanases produced by the chondrocytes through IL-1 mediated mechanism destroy the proteoglycans and weakens the cartilage thereby predisposing for a cartilage destruction. Tissue inhibitor of metalloproteases which is a family of proteins block the activity of metalloproteases by directly binding to them. Degradation of the bone occurs through binding of receptor activator of nuclear factor κ B ligand which is produced by the activated T cells and fibroblast like synoviocytes

with the receptor ,RANK expressed in the osteclasts which in turn will activate the osteoclasts. Osteoprotegerin ,a decoy receptor binds with RANK and competes with RANK-L.Polymorphonuclear neutrophil activation leads to mobilization of membrane phospholipids and release of arachidonic acid metabolites. Proinflammatory product like leukotriene B4 plays a considerable role in in the induction of inflammation.

Clinical features

The clinical manifestations include articular and extra articular features. The articular manifestation may have an insidious onset in 55-65 % of patients, acute onset in 8-15% of patients and subacute in 15-20% of patients. The unusual pattern of onset may be adult onset Still's disease, palindromic onset, polymyalgia rheumatica type and arthritis robustus type. The joints most commonly involved first are metacarpophalangeal joints, proximal interphalangeal joints, metatarsophalangeal joints and wrists. The large joints become symptomatic after the small joints .The extra articular manifestation includes subcutaneous nodules, episcleritis, scleritis, myositis, vasculitis, pulmonary manifestations in the form of pleurisy, interstitial fibrosis, nodular lung disease, bronchiolitis, pulmonary hypertension and small airways disease. Cardiac complications include pericarditis,

myocarditis, endocardial inflammation, conduction defects, coronary arteritis, granulomatous arteritis or valvular disease.

Central nervous system (CNS)

a) Meningeal nodules, pachymeningitis and CNS vasculitis

b) Cervical spine in Rheumatoid arthritis:

- Atlanto Axial Dislocation,
- Subaxial subluxation
- Atlanto Axial Impaction

Peripheral nerve lesions

Chronic or subacute compressive (entrapment) neuropathies

a) Median nerve: Carpal tunnel syndrome is the commonest chronic nerve entrapment neuropathy.
b) Ulnar nerve: Ulnar neuropathy is the second most frequent entrapment neuropathy, the majority occurring at the elbow in the cubital tunnel.

Cervico thoracic nerve roots

Radicular symptoms may be due to rheumatoid involvement of the cervical spine (often silent)

Common peroneal nerves

The common peroneal nerve is vulnerable at the level of the fibular head as the nerve enters the peroneus muscle.

Posterior tibial nerve.

The tarsal tunnel syndrome is not common.

Mononeuritis multiplex

Mononeuritis multiplex is a painful asymmetric asynchronous sensory and motor peripheral neuropathy involving isolated damage to at least 2 separate nerve areas.

Autonomic dysfunction

A wide range of symptoms may indicate abnormal function of the autonomic nervous system.The characteristic autonomic symptoms are

blurred vision due to defective pupillary accommodation, optic nerve or brain ischemia due to orthostatic hypotension, dry eyes or mouth due to impaired parasympathetic innervation to lacrimal or salivary glands, orthostatic light headedness with dull shoulder aching due to muscle ischemia as a result of hypotension; early satiety or alternating diarrhea and constipation due to gastrointestinal dysmotility; and urinary retention or sexual dysfunction due to sympathetic and parasympathetic denervation. Small fiber dysfunction which can cause burning or lancinating pain of the hands and feet, may also cause hypohidrosis, anhidrosis or compensatory hyperhidrosis.

Diagnosis

The diagnosis of RA is by using the 1987 revised American college of rheumatism classification criteria[7] that are based on the effective clinical history and examination, laboratory tests and diagnoses that exclude it.

1987 ACR Criteria for the Classification of Acute Arthritis of Rheumatoid Arthritis [25]

For classification purposes, a patient is said to have RA if he or she has satisfied

at least 4 of the following 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded.

1. Morning stiffness: Morning stiffness in and around the joints, lasting atleast 1 hour before maximal improvement.
2. Arthritis of 3 or more joint areas: Atleast 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician; the 14 possible joint areas are right or left proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, wrist, elbow, knee, ankle, and metatarsophalangeal (MPT) joints.

3. Arthritis of hand joints: At least one area swollen (as defined above) in a wrist, MCP or PIP joint.
4. Symmetric arthritis: Simultaneous involvement of the same joint areas (see 2 above) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).

5. Rheumatoid nodules: Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Serum rheumatoid factor: Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in<5% of normal control subjects.
7. Radiographic changes : Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints(osteoarthritis changes alone do not qualify)

Other organ system involvement includes,

Cardiac	:	Carditis, pericarditis
Pulmonary	:	Pleuritis, Intrapulmonary nodules, Interstitial fibrosis
Hepatic	:	Hepatitis
Ocular	:	Scleritis, Episcleritis, Dryness of the eyes
Vascular	:	Vasculitis
Skin	:	Subcutaneous nodules, ulcers.

The diagnosis of RA should be confirmed or ruled out within 2 months after the onset of synovitis.

Rheumatoid factor:

Rheumatoid factor is the auto antibody reactive with the Fc portion of the IgG. It is found in two third of rheumatoid arthritis. Rheumatoid factor is not specific for rheumatoid arthritis.5% of healthy individual has Rheumatoid factor positivity. Rhematoid factor is not useful as a screening test but can be of prognostic significance[2].

Anti cyclic citrullinated antibody (antiCCP) test:

Anti cyclic citrullinated antibody (anti CCP) test is the latest addition to the list of laboratory investigations. This test is very useful in individual with early rheumatoid arthritis, in whom assessment of anti CCP antibody may be useful to confirm the diagnosis[2].Anti CCP is most common in persons with aggressive disease with a tendency to develop bony erosion[2].Anti CCP antibody is present in 1.5% of normal individuals[2] . It may be positive in 60% of seronegative RA if second generation ELISA kit is used.

Haematological parameters in Rheumatoid arthritis:

Blood count include normocytic normochromic anaemia, normal WBC counts.Thombocytosis, Eosinophilia indicates severe systemic disease.[2]

Imaging studies in Rheumatoid arthritis

Diagnosis of neurological manifestations depend on the type of involvement assessed with the history and clinical examination. Imaging plays an important role in diagnosing the cervical spine and the cerebral lesions. Dynamic x-rays of the cervical spine like lateral view in flexion, extension, neutral may be useful, in diagnosing the atlantoaxial subluxation. CT and MR imaging have a vital role in delineating the involvement of the cervical spine. An atlanto dental distance greater than 3.5 cm is considered abnormal in an adult. Atlanto axial impaction or superior migration of odontoid is diagnosed by using the Mc Gregor's line [8] or Ranawat's index[9] . McGregor's line is drawn from the posterior edge of the hard palate to the most caudal part of the occipital curve of the skull. The tip of the odontoid should be not more than 4.5 mm above the Mc Gregor's line.Another line named Fischgold and Metzger's line[10] is drawn between the two digastric grooves which passes 10.7mm above the tip of the odontoid process

normally. Diagnosis of peripheral nerve lesions requires neurophysiological studies .

Treatment

Treatment of rheumatoid arthritis comprises of non pharmacological and pharmacological therapies. It should have comprehensive regime directed towards treating the basic disease and the complications. Non drug therapy includes patient education, counselling and rehabilitative measures that focus on pain control, patient adherence, rest, joint protection principles and exercise therapy. Drug therapy includes analgesics, nonsteroidal anti-inflammatory drugs, corticosteroids either intra articular or systemic. Systemic steroids which are used as, low dose daily therapy, high dose short course therapy for drug induced thrombocytopenia, mononeuritis multiplex and interstitial lung disease, coronary arteritis. It can be used as a principal therapy during pregnancy when needed. Disease modifying antirheumatic drugs are used according to the algorithmic approach put forward by the American College of Rheumatology. The American College of Rheumatology established recommendations for the use of non biologic and biologic DMARDS in 2008. These guidelines are broken down by disease severity and by duration of disease presence at less than 6 months, 6 months

to 24 months, or greater than 24 months. The use of non biologic DMARDS is recommended early in the management (<6 months) of patients even with low disease activity and no features of poor prognosis. The use of combination DMARD therapy is phased in early and the further consideration of biologic DMARDS is recommended early if there are signs of high disease activity or features of poor prognosis. Nonbiologic DMRDs include methotrexate , glucocorticoids , leflunomide , sulfasalazine, cyclophosphamide, hydroxychloroquine, gold injections, d-penicillamine, minocycline , azathioprine & cyclosporine. Biologic DMARDs include etanercept , adalimumab , abatacept, efalizumab, infliximab , rituximab , and certolizumab.

The combination therapy is supported by the evidence shown in the two trials, COBRA [11] and FIN- RACO [12]. The drugs used in the combination triple drug therapy are methotrexate, hydroxychloroquine and sulphasalazine. Other drugs like leflunomide, cyclosporine, azathioprine, D-penicillamine and gold salts are used either alone or in combination when the conventional DMARD combination therapy fails. The TNF-alpha inhibitors, Etanercept which is a fusion protein of the soluble portion of the human TNF p75 chain of the receptor and the Fc portion of the human

IgG1.This drug is used in patients who fail to respond to first line drugs. INFLIXIMAB a chimeric monoclonal antibody has also been shown to reduce the clinical signs and symptoms along with slowing the radiological progression. ADALIMUMAB is a fully humanized monoclonal antibody against TNF. Other drugs like ABATACEPT, (a fusion protein of CTLA4 with IgG), RITUXIMAB (an anti CD 20) B cell depleting agent have shown to have favorable results on the clinical as well as radiological progression of the disease. ANKINRA(recombinant IL-1 Receptor antagonist)[2] it improves the signs and symptoms of Rheumatoid arthritis. Statins were found to have beneficial effects in RA. Drugs which are under trial include p38 MAP kinase inhibitor, anit B cell stimulator (BLyS) and other anti cytokine therapies.

AUTONOMIC NEUROPATHY

Autonomic neuropathies are a collection of syndromes and diseases affecting the autonomic neurons, either parasympathetic or sympathetic or both . Most often, they occur in conjunction with a somatic neuropathy, but they can also occur in isolation.

The autonomic nervous system modulates numerous body functions; therefore, autonomic dysfunction may manifest with numerous clinical

phenotypes and various laboratory and neurophysiologic abnormalities. A patient may present with symptoms related to a single portion of the autonomic system or both. The degree and type of autonomic system involvement varies extensively. In some patients, the degree of autonomic dysfunction may be subclinical or clinically irrelevant; in others, symptoms may be disabling.

CLASSIFICATION [43]

a) INHERRITED.

b) ACQUIRED,

- PRIMARY.
- SECONDARY.

INHERITED

Familial amyloid polyneuropathy.

Hereditary sensory autonomic neuropathy,

Type 1.
Type 2 (Morvan disease).
Type 3 (Riley-Day syndrome or familial dysautonomia).
Type 4.
Type 5.

Fabry disease.

Acute intermittent porphyria & variegate porphyria.

ACQUIRED

Primary acquired

Pandysautonomia.

Idiopathic distal small-fiber neuropathy.

Holmes-Adie syndrome and Ross syndrome:

Chronic idiopathic anhidrosis.

Amyloid neuropathy.

Postural orthostatic tachycardia syndrome.

SECONDARY ACQUIRED

Metabolic derangements,

Diabetes mellitus.

Uremic neuropathy.

Hepatic disease–related neuropathy.

Vitamin deficiency and nutrition-related neuropathy:eg vit b_{12} deficiency

Toxic and drug-induced autonomic neuropathy.

Alcohol.

Infectious diseases,

Lyme disease.
HIV infection.
Chagas disease.
Botulism.
Diphtheria.
Leprosy.

Autoimmune conditions,

Rheumatoid arthritis.
systemic lupus erythematosus.
Celiac disease.
Sjögren syndrome.

Guillain-Barré syndrome.

Lambert-Eaton myasthenic syndrome.
Paraneoplastic autonomic neuropathy.
Inflammatory bowel disease.

Symptoms due to autonomic dysfunction[43]

OCULAR	RENAL
• Blurring then graying of vision. • Blacking out. • Tunnel vision. • Sensitivity to light. • Difficulty with focusing. • Reduced lacrimation. • Loss of pupillary size over time (which is often correlated with loss of visual symptoms).	• Nocturia. • Bladder urgency. • Bladder frequency. • Enuresis. • Incomplete bladder voiding. • Urinary retention. • Urinary incontinence.

GASTROINTESTINAL	SEXUAL
• Constipation. • Episodic diarrhea. • Early satiety. • Increased gastric motility. • Dysphagia. • Bowel atony. • Bowel incontinence. • Gastroparesis in diabetes mellitus (which may cause food stasis and subsequentvomiting)[41] • Hyposalivation. • Altered sense of taste.[42]	• Impotence. • Loss of ejaculation, and retrograde ejaculation in men. • Inability to achieve orgasm or nonspecific sexual dysfunction in both sexes.
	Sweating & Temperature regulation
	• Anhydrosis or hypohidrosis compensatory hyperhidrosis, & gustatory sweating.[41] • Hypothermia (from loss of shivering and inability to vasoconstrict to prevent heat loss) and hyperpyrexia.

CARDIOVASCULAR	
• Orthostatic onset of palpitations. • Nausea. • Tremulousness. • Presyncope with light-headedness. • Visual blurring, tinnitus. • Headache.	• Chest pain, and shortness of breath. • (Elderly patients may complain of coat hanger or lower extremity discomfort. These symptoms may be worse after a large meal or in severe illness.

RESPIRATORY SYSTEM
• Impaired control of bronchomotor tone leading to a depressed bronchoconstrictory response to cholinergic stimuli (caused by diabetes mellitus). • Impaired ventilatory and heart rate response to hypoxia but not to hypercapnia, in patients with diabetes.
EXTREMITIES
• Burning feet most commonly observed in small-fiber sensory neuropathy. • Pruritus. • Dysesthesia. • Allodynia. • Hyperalgesia. • Nocturnal exacerbation of symptoms. • Dry skin, and loss of distal leg hair. • Brittle nails, pallor, and cold feet.

CARDIAC AUTONOMIC NEUROPATHY(CAN)

CAN is manifested by abnormal heart rate, blood pressure, and redistribution of blood flow . The cardio vascular anomalies of autonomic neuropathy involve both the sympathetic and parasympathetic nervous systems[15.] The pathogenesis of the ANS dysfunction in patients with RA is not clearly understood. Vasculitis of the vasa nervorum and secondary amyloidosis has been proposed.[25] The pathogenesis may have an immune component. The presence of circulating autoantibodies against nerve growth factor, (the trophic factor for the development and survival of sympathetic and sensory neurons), cervical ganglia and the vagus nerve has been recently demonstrated in RA patients who had cardiovascular ANS dysfunction.[6,16] The significance of these auto-antibodies in the pathogenesis of ANS dysfunction remains to be determined. The auto antibodies occurred independendly of the presence of other conventional antibodies, thus indicating that their target antigens are tissue specific. The nature of these auto antigens remained to be determined. The supportive evidence of an immune component in the pathogenesis of the autonomic dysfunction in rheumatoid arthritis is the pathological finding of a perivascular

lymphocytic infiltrate in sympathetic ganglia section of two patient with rheumatoid arthritis..[6]

Three major syndromes (cardiac denervation, exercise intolerance, and orthostatic hypotension) are associated with dysfunction of the cardiovascular autonomic nervous system [18,17]. Patients with CAN have higher resting heart rates and lower maximal heart rates during exercise than patients without autonomic neuropathy [19] The sole manifestation of asymptomatic reduced heart-rate variability does not appear to be associated with premature mortality.[20] Symptomatic autonomic neuropathy however has been shown to have a poorer prognosis, revealing a 10-year mortality rate of approximately 27%.[20] Those with symptomatic autonomic neuropathy may be at a higher risk of mortality compared to patients with asymptomatic autonomic neuropathy, because they may be part of a subgroup with other complications and thus more advanced disease.[21] Abnormal autonomic function is known to predispose to arrhythmogenesis in clinical and experimental conditions. The loss of HRV and sympathovagal imbalance (either increased sympathetic or reduced vagal activity) has been shown to be a strong and independent predictor of postinfarction mortality and is of prognostic value in patients with heart failure and diabetic neuropathy . Conversely, vagal predominance could exert protective and

antifibrillatory effects [22]. The relative predominance in sympathetic tone plays a key role in the development of ventricular tachyarrhythmia. Indeed, in a recent long-term follow-up study on the cause of death in patients with RA, more sudden deaths were found in RA patients than in controls. Riise et al. reported that sudden deaths accounted for 11.3% of total mortality in patients with RA [17].

Unexplained sudden death not associated with myocardial infarction, in which the heart becomes unresponsive to nerve impulses (cardiac denervation syndrome), has been reported in patients with CAN [23,24]. Other Complication of CAN includes Silent Cardiac Ischemia, Arrhythmias, Sudden Cardiac Death, LV Hypertrophy, Altered Coronary Vasomotor Dynamics, Platelet Stickiness.

Three of the most widely used tests for the determination of CAN include RR-variation during deep breathing, the Valsalva manoeuvre, and blood pressure response to standing.[25] According to the American Academy of Neurology, these are established tests, meaning that they are "accepted as appropriate by the practicing medical community for the given indication in the specified patient population" [26]. Resting heart rate is primarily controlled by the parasympathetic system, whereas maximal heart rate and blood

pressure responses to standing[27] sustained hand grip, and other types of exercise are mainly functions of sympathetic activity (which controls blood vessel tone).Though test using cardiovascular reflex are most often done on diabetics, they are equally applicable in the diagnosis of autonomic damage caused by other disorder [28,29].

Variables Influencing CAN testing

1) Time of the day
2) Metabolic Status
3) Coffee & Smoking Avoidance
4) Presence of Cardiovascular disease & drugs
5) Posture - Standing and sitting reduces HRV

In our study we used the Ewings battery of cardiovascular tests to detect cardiac autonomic neuropathy: The tests can be divided in to

A Tests reflecting cardiac parasympathetic damage:

1.Heart rate response to Valsalva manoeuvre. The Valsalva manoeuvre is a much more complex reflex arc involving sympathetic and parasympathetic pathways to the heart, sympathetic pathways to the vascular tree, and

baroreceptors in the chest and lungs.[25] There are four phases in valsalva cardiovascular responses include

- Phase I Rise in BP
- Phase II ↓ in BP ; Tachycardia.
- Phase III Fall in BP
- Phase IV Overshoot of BP; Bradycardia

During the strain period of the valsalva manoeuvre the blood pressure drops and heart rate rises. After release the blood pressure rises, overshooting its resting value, and the heart slows. The heart rate response in valsalva is mediated by vagus nerve[29]. In patients with autonomic neuropathy the blood pressure slowly falls during the strain and slowly return to normal after the release, with no overshoot rise in blood pressure and no change in heart rate. The test was performed by the patient blowing into a mouth piece connected to a sphygmomanometer and holding it at a pressure of 40 mm Hg for 15 seconds while a continuous ECG was recorded. The manoeuvres performed 3 times with interval of one minute in between. The result was expressed as the Valsalva ratio[30] which is the ratio of the longest R-R interval after the manoeuvre (reflecting overshoot bradycardia following release) to the shortest R-R interval during the

manoeuvre.(reflecting the tachycardia during strain) The mean of three Valsalva ratio was taken as the final value

VALSALVA RATIO		POINTS
>1.21	Normal	0
1.11 - 1.20	Borderline	0.5
<1.10.	Abnormal	1

2) Heart rate variation during deep breathing

Normally the heart rate varies continually but it depends upon intact parasympathetic nerve supply. Patients with autonomic neuropathy may have a noticeable reduction in and sometimes complete absence of heart-rate variation. Reduced heart rate variability is the earliest indicator of cardiovascular autonomic neuropathy [31]

Autonomic imbalance associating increased sympathetic activity and reduced vagal tone has been been strongly implicated in the pathophysiology of arrhythmogenesis and sudden cardiac death. Among the different available noninvasive techniques for assessing the autonomic status heart

rate variability (HRV) has emerged as a simple, non invasive method to evaluate the sympathovagal balance at the sinoatrial level.[32] and as a clinical tool for screening and identifying patients particularly at risk for cardiac mortality.[32]

The patient sits quietly and breathes deeply at 6 breaths a minute (five seconds in and five seconds out) for one minute. Deep breathing at six breath per minute is the most convenient and reproducible technique [19] An electrocardiogram was recorded throughout the period of deep breathing with a marking done to indicate the onset of each inspiration and expiration. The maximum and minimum RR intervals during each breathing cycle were measured and converted into beats/minute. The result was then expressed as the mean of the difference between maximum and minimum heart rates for the 6 measured cycles in beats a minute

HEART RATE VARIATION DURING DEEP BREATHING		**POINTS**
> 15 beats / minute	normal response	0
11-14 beats / minute,	borderline	0.5
< 10 beats / minute.	abnormal response	1

3) Immediate heart rate response to standing (30:15 ratio)

During the change from lying to standing a characteristic immediate rapid increase in heart rate occur which is maximal at about the 15th beat after standing. A relative overshoot bradycardia then occur, maximal at about the 30th beat. This response is mediated by vagus nerve. Patients with autonomic neuropathy show only a gradual or no increase in heart rate after standing.

The test was performed with the patient lying quietly on a couch while heart rate was recorded continuously on ECG machine. The patient was asked to stand up unaided and the point at starting to stand was marked on ECG. The shortest R-R interval at or around the 15th beat and largest R-R interval at or around the 30th beat after starting to stand were measured with a ruler. The characteristic heart rate response was expressed by 30:15 ratio, values are as follows

IMMEDIATE HEART RATE RESPONSE TO STANDING		**POINTS**
> 1.04	Normal	0
1.01- 1.03	Borderline	0.5
< 1.00	Abnormal	1

B) Tests reflecting sympathetic damage:

1) Blood pressure (BP) to standing

On standing pooling of blood in the legs causes a fall in blood pressure ,which is normally rapidly corrected by peripheral vasoconstriction[29] In patients with autonomic neuropathy the blood pressure falls on standing and remains lower than in lying position. The test was performed by measuring the patients BP while he was lying down quietly and again when he stood up. The postural fall in BP was taken as the difference between systolic BP lying and the systolic BP standing values are given below

SYSTOLIC BLOOD PRESSURE FALL ON STANDING		POINTS
<10	Normal	0
11-30	Boderline	0.5
>30	Abnormal	1

2) Blood pressure response to sustained hand grip

During sustained handgrip a sharp rise in blood pressure occurs , due to a heart rate dependant increase in cardiac output with unchanged peripheral resistance. In patients with autonomic neuropathy, rise in diastolic blood pressure is abnormally small. The maximum voluntary contraction is first determined using a handgrip dynamometer. Handgrip is then maintained at 30% of that maximum for as long as possible up to 3 mts. Blood pressure is measured three times before and at one minute interval during handgrip. The result is expressed as the difference between the highest diastolic blood pressure during hand grip exercise and the mean of the three diastolic blood pressure reading before handgrip began

INCREASE IN DIASTOLIC BP DURING SUSTAINED HANDGRIP		POINTS
>15 mmof Hg	Normal	0
15-10 mm of Hg	Boderline	½
<10 mmof Hg	Abnormal	1

RESULTS OF CARDIOVASCULAR REFLEX TEST

The total points from each of these five tests are added together and the cardiac autonomic neuropathy score calculated (CAN score). Based on the CAN SCORE categorized as follows:

CAN SCORE	TOTAL POINTS
0 or ABSENT CAN	0
1 or EARLY CAN	0.5-1.5
2 or DEFINITE CAN	2-3
3 or SEVERE CAN	>3.5

AIM OF THE STUDY

1) To study the prevalence of cardiac autonomic neuropathy in patients with Rheumatoid arthritis

2) To study the correlation between cardiac autonomic neuropathy and Age, Sex, Duration of disease, Rheumatoid factor positivity and the DAS 28 score.

MATERIALS

Fifty three patients (15 males, 38 females) with rheumatoid arthritis who attended the outpatient department of rheumatology, Madurai Medical College were included as the study population. Twenty nine age and sex matched persons were taken as controls. This is a cross-sectional- case control study conducted for a period of 6 months . The study patients were below 60 years of age so that the neurological problems due to ageing was minimized .After detailed history, clinical examination and lab investigations, other causes of autonomic neuropathy were excluded and then cardiac autonomic reflex test done .All patients were able to perform cardiac autonomic reflex test . Few patients had difficulty in exerting maximum hand grip in dynamometer. But they were able to achieve 30% of the maximum hand grip for the age and sex matched control. The controls were selected from the healthy relatives of the patients and those attended OPD with minor ailments like URTI. Informed consent taken from both patients and control before assigning them to study

Inclusion criteria

Patients who fulfilled 1987 revised AMERICAN RHEUMATOLOGY ASSOCIATION criteria for rheumatoid arthritis.

Exclusion criteria

1) Age above 60 years

2) Endocrine and Metabolic disorders like Diabetes and Electrolyte imbalance like Hyponatremia and Hypokalemia

3) Hypertension

4) Liver, Renal, Respiratory and Cardiac diseases

5) Pregnancy

6) Severe anemia

7) Treatment with drugs influencing the adrenergic nervous system like beta blockers, antiarrhythmic agents, diuretic, adrenergic inhibitor, vasodilator, sedative, hypnotic and antiepileptic drugs were also excluded from the study.

8) Cardiac disease like CAD, CCF, arrythmias, cardiomyopathy, volume overload status

9) Presence of central or peripheral nervous system disease CVA, leprosy

10) Presence of any other disease that affects the ANS like hypothyroidism, amyloidosis, systemic lupus erythematosis, multiple myeloma

METHODS

All the selected patients were subjected for detailed clinical examination.

Hematological evaluation included complete hemogram,

Biochemical parameters including blood urea, serum creatinine, serum sodium, serum potassium, Liver function test, TFT, Random blood sugar

Immunological evaluation included Rheumatoid factor and CRP by latex agglutination method.

Cardiac autonomic neuropathy testing.

Five standard cardio vascular autonomic reflex tests (Ewings et al ,1970)[4] which assess the integrity of sympathetic and parasympathetic system on cardiovascular system were done..These tests include

1. Heart rate response to deep breathing (E/I ratio)
2. Heart rate response to valsalva manoeuvre
3. Immediate heart rate response to standing(30:15)
4. Blood pressure response to sustained handgrip
5. Blood pressure response to standing

First three tests assessed parasympathetic system and the rest two assessed sympathetic function. Parasympathetic system assessment done by taking continuous ECG monitoring with 8-channel PSYCO-PHYSIOPAC software and by calculating the heart rate and ratio by using the standard guidelines as described below. Sympathetic system assessed by measuring the blood pressure in standing and sustained hand grip using dynamometer and mercury manometer.

TEST PROTOCOL

Tests were done during the morning hours

Tobacco, Alcohol were not allowed before the test

Patients were asked to relax in a quiet room for at least 10 minutes before testing. Then tests were conducted, in the following order. First supine BP is measured and maximum power in dynamometry assessed, then ECG limb leads connected and continous ECG recording done at lead 2 in 8-channel psyco-physiopac software. Time is noted separately during the start of each phase like beginning and ending point of inspiration ,beginning of strain phase of valsalva and release phase,30^{th} and 15^{th} beat after immediate standing etc, so as to calculate heart rate at various phases. Recording done at first during normal breathing for 30 seconds, then deep breathing for one minute, then instructed to take normal breathing again for 30seconds, after this valsalva manoeuvre done as described in further section. After valsalva manoeuvre is over, patient takes normal breathing for 30 seconds and then asked to stand immediately. Once 30^{th} QRS complex is over in ECG recording after standing, recording is stopped .Then Blood pressure measured at 3^{rd} minute of standing from supine position. (Recording at

normal breathing done in between to get a stable base line heart rate between each events) .Then patient lies in supine position, Blood pressure measured, and after one minute hand grip BP measured by using grip dynamometer with 30% of maximum power.

1.HEART RATE RESPONSE TO DEEP BREATHING

The patient is made to lie in supine position quietly and breathe at the rate of six breaths per minute for one minute. ECG is recorded throughout the period of deep breathing, with time noted separately to indicate the onset of each inspiration and expiration using 8-channel psyco-physiopac.The maximum and minimum heart rate during each breathing cycle is measured. The result is then expressed as the mean of the difference between maximum and minimum heart rate for the six measured cycles.

2. HEART RATE RESPONSE TO VALSALVA MANOEUVRE

The patient is asked to blow in to the rubber tubing of the sphygmomanometer and hold it at pressure of 40 mm of mercury for 15seconds while continuous ECG was recorded. Then the patient was asked to breathe normally with continuous ECG monitoring. The manoeuvre is perfomed thrice, with one minute interval in between them. Then valsalva

ratio is calculated, which is the ratio of the maximum heart rate during the release phase to the minimum heart rate during the straining phase .

3. IMMEDIATE HEARTRATE RESPONSE TO STANDING

The test is performed with the patient lying quietly, while a continuous ECG being recorded. The patient is then asked to stand up immediately and the starting time of standing is noted separately. the shortest RR interval at or around the 15^{th} beat and the longest RR interval at or around the 30^{th} beat after standing are measured .The result is expressed as the ratio of RR interval of 30^{th} to 15^{th} (30:15 ratio)

4. BLOOD PRESSURE RESPONSE TO STANDING

Measuring patient's blood pressure twice, first in lying posture and the second at standing .The standing blood pressure is taken after an interval of three minutes of standing. The blood pressure response is the difference in systolic pressure on lying and on standing. The test is repeated thrice and the average of 3 values is taken into account

5 BLOOD PRESSURE RESPONSE TO SUSTAINED HANDGRIP

The maximum voluntary contraction of hand is determined using grip dynamometry initially and the hand grip test is done by maintaining the

grip at 30% of the maximum up to three minutes using dynamometer. The result is expressed as the difference between the highest diastolic blood pressure during the hand grip and the normal diastolic blood pressure before the hand grip.

The results of each of the above five tests are classified into three separate groups based on the severity of abnormality detected, and each of them is given a definite point as described by Bellavere et al.

TABLE:1 DETERMINATION OF CAN SCORE

Autonomic function test	**Points**
1 Heart rate variability on deep breathing	
>15 beats/min	0
11-15 beats/min	1/2
<11 beats/min	1
2. Postural hypotension (fall in systolic blood pressure)	
<10 mm Hg	0
11-29 mm Hg	1/2
>30 mm Hg	1
3. Valsalva ratio (longest RR interval: shortest RR interval)	
>1.2	0
1.2–1.10	1/2
<1.10	1
4. Heart rate variability on standing(30:15)	
>1.04	0
1.01-1.03	1/2
<1	1
5. Increase in diastolic blood pressure during sustained handgrip	
>15 mm Hg	0
15–10 mm Hg	1/2
<10 mm Hg	1

The total points from each of these five tests are added together and the cardiac autonomic neuropathy score calculated (CAN score). Based on the CAN SCORE categorized as follows:

CAN SCORE	TOTAL POINTS
0 or ABSENT CAN	0
1 or EARLY CAN	0.5-1.5
2 or DEFINITE CAN	2-3
3 or SEVERE CAN	>3.5

DAS 28 score

Disease activity score is a composite score using tender and swollen joint count, ESR and patient's global assessment activity using a 10 mm visual analogue scale.

DAS28= 0.56 √(tender joints) + 0.28√(swollen joints)

+ 0.70 Log (ESR) + 0.014(VAS in mm)

Classification

Less Active ≤ 3.1

Moderate 3.2- 5.1

Highly active > 5.1

(Minimum score= 0; Maximum score= 9)

STATISTICAL ANALYSIS

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2008).**

Using this software, range, frequencies, percentages, means and standard deviations and p value were calculated.

RESULTS AND ANALYSIS

A total of 53 patients were evaluated.All of the patients are from Madurai district only. The male : female ratio is 1:2.5. The mean age is 40.5±7.7years. Mean duration of the disease was 6.51±3.52 yrs.

Out of 53 patients, four patient had postural dizziness (1 male and 3 female)

Laboratory evaluation showed,

Hb ranges from 10 gm% to 12.6 gm%, with Mean Hb of 10.96± 0.64gm%.

ESR ranges from 25-120 mm with mean of 63.3±27.8 mm/ 1^{st} hr

Rheumatoid factor (RF) was positive in 39 (73.6%) patients..

CRP Positive in 35 (66.1%).

DAS 28 was in the range of 3-8.26 with a mean of 6.5.

Out of 53 patients who were subjected for autonomic nervous system tests, 18 (34%) patients had CAN score ≥2 ie, DEFINITE CAN.

PROFILE OF PATIENTS WITH DEFINITE CARDIAC AUTONOMIC NEUROPATHY ARE AS FOLLOWS,

Fourteen patients were females and four were males.

The mean age was 41.4±7.6 years.

The mean disease duration was 6.8±3.9 yrs.

The Mean Hb is 10.94±0.53gm%.

The mean DAS 28 score was 6.5±1 was there in can positive patients.

RF positivity is present in 13 patients and 12 patients is having CRP positivity.

The mean ESR is 68.9±31.4mm/hr.

PROFILE OF CASE STUDIED

Table 1 Sex Distribution Among Cases And Control

SEX	CASES		CONTROL	
	NO	%	NO	%
MALE	15	28.3	10	32.3
FEMALE	38	71.7	21	67.7
TOTAL	53	100	31	100
P VALUE	0.8491 NOT SIGNIFICANT			

There is no statisticallty significant relation ship between sex distribution among cases and control (p= 0.8491)

Table 2 Age Distribution In Cases And Control

AGE IN YEARS	CASES		CONTROL	
	NO	%	NO	%
<30	4	7.5	5	16.1
30-39	19	35.8	12	38.7
40-49	23	43.4	10	32.3
50 & ABOVE	7	13.2	4	12.9
TOTAL	53	100	31	100
RANGE	21-56		25-58	
MEAN	40.5		38.8	
SD	7.7		8.7	
P VALUE	0.2837 NOT SIGNIFICANT			

Mean age is 40.5 among cases, and 38.8 among control. There is no statistically significant relation ship between age distribution among cases and control (p = 0.2837)

Table 3 Quantitative Parameters

PARAMETER	RANGE	MEAN	SD
DURATION	1-15yrs	6.62	3.74
HB	10-12.6	10.96	0.64
ESR	25-120	63.3	27.8
DAS28	3-8.26	6.28	1.31

MEAN DAS28 IS 6.28

Mean duration is 6.62years

Table 4(a) Qualitative Parameters

PARAMETER	POSITIVE		NEGATIVE	
	NO	%	NO	%
RF	39	73.6	14	26.4
CRP	35	66.1	18	33.9

Among the 53 cases 39 were Rheumatoid factor positive and 35 were CRP positive.

Table 4(b): Disease Duration Among Cases

Duration	Cases	
	NO	%
0-5	23	43.4
6-10	22	41.5
10-15	8	15.1
TOTAL	53	100

Most of the patients are in the disease duration category of 0-10 years .

Table 4(C): Das 28 Distribution Among Cases

DAS28 SCORE	NO: OF PATIENTS
≤3	1
3.1-5	11
>5	41

Majority of the cases ie, 77 % in our study comes under the DAS28 category is >5

Table 5: can score distribution

CAN SCORE	CASES	
	NO	%
NO CAN	4	7.5
EARLY CAN	31	58.5
DEFINITE CAN	18	34
TOTAL	53	100

Among 53 cases 18 (34%) had DEFINITE CARDIAC AUTONOMIC NEUROPATHY

Table 6 Definite CAN And Age Group

AGE GROUP	TOTAL	DEFINITE CAN			
		POSITIVE		NEGATIVE	
		NO	%	NO	%
<30	4	1	25	3	75
31-40	19	6	31.6	13	68.4
41-50	23	9	39.1	14	60.9
>50	7	2	28.6	5	71.4
TOTAL	53	18	34	35	66
MEAN	41.4			40	
SD	7.6			7.8	
P VALUE	O.5916 NOT SIGNIFICANT				

Most of the definite cardiac autonomic neuropathy patients comes under the age group of 41-50 ie (39.1%) but p = 0.596 , suggesting that definite can and age has no statistically significant relation.

Table 7 Definite Can And Sex

SEX	TOTAL	DEFINITE CAN			
		POSITIVE		NEGATIVE	
		NO	%	NO	%
MALE	15	4	26.7	11	73.3
FEMALE	38	14	36.8	24	63.2
TOTAL	53	18		35	
P VALUE	0.702 NOT SIGNIFICANT				

Most of the definite cardiac autonomic neuropathy patients are ie (39.1%) females. but p = 0.702, suggesting that definite can and sex has no statistically significant relation.

Table 8 Definite CAN and duration of disease

DURATION OF DISEASE	TOTAL NO AMONG EACH DURATION SCALE	DEFINITE CAN			
		POSITIVE		NEGATIVE	
		NO	%	NO	%
<5	18	7	38.9	11	61.1
5-10	27	8	29.6	19	70.4
>10	8	3	37.5	5	62.5
TOTAL	53	18	34	35	66
MEAN		6.8 YEARS		6.5 YEARS	
S.D		3.9 YEARS		3.7 YEARS	
P VALUE	0.88 NOT SIGNIFICANT				

For definite cardiac autonomic neuropathy and duration of illness p = 0.88, suggesting that definite can and duration of disease has no statistically significant relation.

Table 9: Definite CAN And RF

RF	NO. OF CASES	DEFINITE CAN			
		POSITIVE		NEGATIVE	
		NO	%	NO	%
POSITIVE	39	13	33.3	26	66.7
NEGATIVE	14	5	35.7	9	64.3
P VALUE	0.5596 NOT SIGNIFICANT				

For definite cardiac autonomic neuropathy and RF positivity p = 0.5596, suggesting that definite can and RF positivity has no statistically significant relation.

Table 10 Definite CAN And CRP

CRP	NO. OF CASES	DEFINITE CAN			
		POSITIVE		NEGATIVE	
		NO	%	NO	%
POSITIVE	35	12	34.3	23	65.7
NEGATIVE	18	6	33.3	12	66.7
P VALUE	0.8127 NOT SIGNIFICANT				

For definite cardiac autonomic neuropathy and CRP positivity p = 0.8127, suggesting that definite can and CRP positivity has no statistically significant relation

Table 11 Definite CAN And DAS28

DAS 28	DAS28			
	POSITIVE		NEGATIVE	
	NO	%	NO	%
<3	0	0	1	2.9
3.1-5	2	11.1	9	25.7
>5	16	88.9	25	71.4
TOTAL	18	34	35	66
MEAN DAS 28	6.5		6	
S.D	1		1.3	
P VALUE	0.62 NOT SIGNIFICANT			

For definite cardiac autonomic neuropathy and DAS28 p = 0.62. suggesting that definite can and DAS28 has no statistically significant relation.

Table 12 Definite And HB

PARAMETER	AVERAGE VALUE IN		P VALUE
	CAN POSITIVE	CAN NEGATIVE	
	MEAN ± SD	MEAN ± SD	
HB	10.94 ±0.53	10.97 ± 0.7	0.8279 NOT SIGNIFACANT

For definite cardiac autonomic neuropathy and Hb p = 0.8279. suggesting that definite CAN and Hb has no statistically significant relation.

Table 13 Ewings Battery Of Test Results In Patients And Control

PARAMETER	STUDY	CONTROL	P VALUE
	MEAN±SD	MEAN±SD	
HR REST	79.9 ± 8.5	75.5± 4.9	0.0272
HR DB MAXIMUM	89.6±8.8	90±5.5	0.7872
HR DB MINIMUM	77.5±9.5	68.1±4.6	0.0001
HR VARIABILITY	12.1±6.9	21.9±3.7	0.0001
VAL MAX	99±11.7	98.1±4	0.6283
VAL MINI	76.4±9.4	66.1±4.4	0.0001
VAL RATIO	1.31±0.19	1.49±0.09	0.0001
30:15	1.03±0.06	1.08 ±0.02	0.0367
SYSTOLIC FALL IN BP ON STANDING	11.06±6.76	7.94 ± 3.67	0.048
HAND GRIP DBP DIFFERENCE	11.68±6.23	17.23±2.72	0.0001

Heart rate variability during deep breathing, Valsalva ratio, and rise in diastolic BP during sustained hand grip are more significantly decreased in the study

DISCUSSION

A total of 53 patients were evaluated in our study. All of the patients are from in and around Madurai district only. The Male : Female ratio is 1:2.5. The mean age is 40.5±7.7 years. Mean duration of the disease was 6.51±3.52 yrs. Out of 53 patients four patient had postural dizziness (1 male and 3 female)

Laboratory evaluation showed,

Hb ranging from 10 gm% to 12.6 gm%, with Mean Hb of 10.96± 0.64 gm%. ESR ranging from 25-120 mm with mean of 63.3±27.8 mm/ 1st hr Rheumatoid factor (RF) was positive in 39 (73.6%) patients..

CRP was positive in 35 (66.1%).

DAS 28 was in the range of 3-8.26 with a mean of 6.5.

Out of 53 patients who were subjected for autonomic nervous system tests, 18 (34%) patients had CAN score ≥2 so they were assigned under DEFINITE CAN in the Bellavere modification of Ewings test category.

Profile of patients with DEFINITE CAN in our study	
M : F	4:14
MEAN AGE	41.4±7.6 years
MEAN DISEASE DURATION	6.8±3.9 yrs.
RHEUMATOID FACTOR +ve	13 patients
CRP +ve	12 patients
MEAN DAS28	6.5±1
MEAN Hb	10.94±0.53gm%.
MEAN ESR	68.9±31.4mm/hr

The results were analysed and DEFINITE CAN group were correlated with age of the patient ,sex of patient ,disease duration and Rheumatoid factor positivity and disease severity score(DAS28)

CAN correlation with various parameters		
	P value	
CAN and AGE	0.5916	not significant
CAN and SEX	0.702	not significant
CAN and DURATION OF DISEASE	0.88	not significant
CAN and RHEUMATOID FACTOR POSITIVITY	0.5596	not significant
CAN and DAS 28	0.6	not significant

Our study shows that 34% (ie 18 patient out of 53 RA patients) of rheumatoid arthritis have cardiac autonomic neuropathy. Among patients with cardiac autonomic neuropathy only four patient (22%) have symptoms of cardiac autonomic neuropathy and the remaining ie, 14 patients (78%) of them are asymptomatic. Correlating our study results with the age ,sex, duration of disease,DAS28, rheumatoid factor positivity and CRP , it was found that there is no statistically significant relationship between CAN and these parameters. Among the reflex tests valsalva ratio, and Expiration:inspiration ratio and diastolic BP in handgrip had the high significance value.

Similar studies conducted in various centers showed little variation in the percentage of cardiac autonomic neuropathy in the study population but uniform finding in these studies is that cardiac autonomic neuropathy has no statistically significant relationship with age, sex, duration of disease, rheumatoid factor positivity or DAS 28.

LOUTHRENOO, et al studied CAN IN RA among 34 RA patients[33] with M:F 1:7.5, age group were 47.2±10.5 and duration of disease was 5.1±3.6[1] This study used standard Ewings test for assessing the cardiac autonomic status . In this study 47% of the RA Patients have diminished

cardiovascular ANS responses .It showed no correlation to number of Swollen joints, ESR ,RF titre or Duration of disease.

V. Sandhu et al studied about Attenuated cardiovascular reflexes in established RA,in 62 patients with 41 healthy age and sex matched control. In this study age was 38±8.4yrs[34]. .This study showed that Valsalva ratio, Heart rate variation during deep breathing, 30:15 ratio, Diastolic blood pressure response to hand grip were significantly decreased in rheumatoid arthritis patient.

The following are the p value for the standard cardiovascular test The Valsava ratio (VR)(p=0.03),The heart rate variation during deep breathing (HRV) was (p=0.01),The 30:15 ratio in entire RA cohort (p=0.001) . The diastolic blood pressure response to hand grip in RA patients (p=0.001), No abnormalities were found in the systolic blood pressure response to standing. In RA patients in this study, the lowest values for VR, HRV and 30:15 were recorded in those with disease of greater than 10 years duration. However, on multivariate analysis, neither age nor duration of disease nor seropositivity[35] was found to be an independent variable predicting impaired cardiovascular reflexes

In a study conducted by Toussirot E et al[38].cardiac autonomic dysfunction was reported to be 60%. who demonstrated that 60% of their 50 RA patients had ANS dysfunction, defined by abnormal results on two of the three cardiovascular reflex tests. However, ANS dysfunction showed no correlation with the Duration of the disease, Inflammatory syndrome, RF titre or Articular destruction.

In Carşamba Government Hospital, Turkey, M. Aydemir et al studied cardiac autonomic profile in rheumatoid arthritis in 26 RA patients[36] with 40 healthy controls. Autonomic nervous system dysfunction was determined according to classical Ewing autonomic test battery and modified Ewings criteria . Both the classical and modified Ewing test batteries have revealed that the frequencies of autonomic neuropathy were significantly higher in patient groups compared with controls ($p < 0.001$). . No relation was found between autonomic neuropathy and disease duration, disease activity and autoantibody positivity.

Bidikar MP[37] et al j studied sympathetic nervous system involvement in fifty rheumatoid arthritis patient between age group of 20 to 60 yrs by using

standard test and found out that 26% of rheumatoid arthritis patient had sympathetic dysfunction

Maule et al.,[6] also showed impaired autonomic nervous function in patients with RA. They reported that auto antibodies directed against autonomic nervous system structures might play a role in the pathogenesis of the autonomic dysfunction.[6]

Tan *et al.*[39] also found abnormal heart rate response to deep breathing in eight of their 30 RA patients (27%). Five of these eight had had clinical symptoms of dysautonomia.

Edmonds *et al*[40]demonstrated abnormalities in parasympathetic cardiovascular reflexes in nine of their 27 RA patients (33%).

SUMMARY

The study on "CARDIAC AUTONOMIC NEUROPATHY IN RHEUMATOID ARTHRITIS" is a cross sectional–case control study conducted on patients visiting outpatient Department of Rheumatology, Government Rajaji Hospital,Madurai.

Our aim was to study the prevalence of CARDIAC AUTONOMIC NEUROPATHY in rheumatoid arthritis and to correlate with the AGE, SEX, DURATION OF ILLNESS, RHEUMATOID FACTOR POSITIVITY, CRP, and DAS28 SCORE.

Fifty three patients with rheumatoid arthritis and twenty nine age and sex matched control were studied. Cardiac autonomic function test is done by EWINGS STANDARD CARDIOVASCULAR REFLEX TEST and scoring done according to Bellevare modification of Ewings criteria.

The information collected regarding all the selected cases and control were recorded in a master chart and data analysis done with the help of Epidemiological Information Package (EPI 2008)

Analysis of data shows that DEFINITE CARDIAC AUTONOMIC NEUROPATHY (CAN) ie., at least two abnormal test in the EWINGS

STANDARD CARDIOVASCULAR TEST, was present in 18 (34%) patient. On correlating DEFINITE CAN positive patients data with the Age, Sex, Duration of illness, RF positivity, DAS 28 and CRP, it was found that there is no statistically significant correlation between DEFINITE CAN and these parameters.

Our study had only 53 patients and a study on larger population could throw more light on the cardiac autonomic neuropathy in rheumatoid arthritis

CONCLUSION

- Cardiac autonomic neuropathy is a common manifestation in patients with rheumatoid arthritis
- More than 3/4th of the cardiac autonomic neuropathy are asymptomatic
- Cardiac autonomic neuropathy has no relation with age, sex, seropositivity, duration of illness or DAS 28
- This study emphasizes the need for an early screening for cardiac autonomic neuropathy in rheumatoid arthritis to avoid morbidity and mortality and to anticipate cardiovascular responses in procedures like general anaesthesia and surgical procedures

RESEARCH LAB –INSTITUTE OF PHYSIOLOGY

MADURAI MEDICAL COLLEGE

PHYSIOLAB -- 8-channel PSYCO-PHYSIOPAC

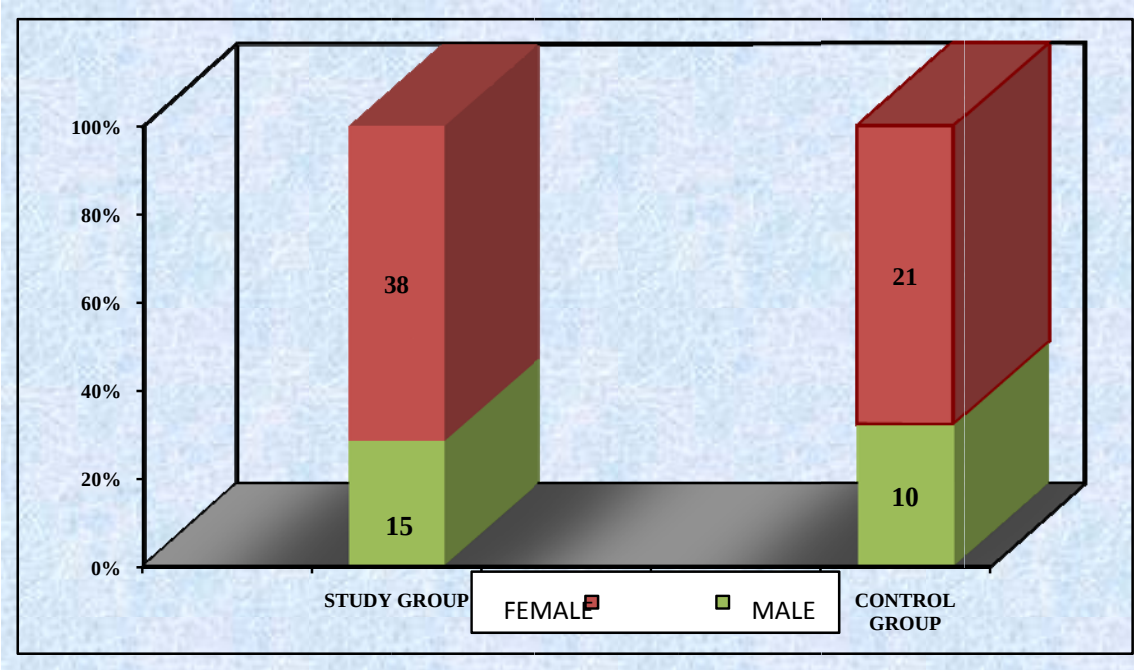
GRIP DYNAMOMETER

MATERIALS USED FOR CAN TESTING

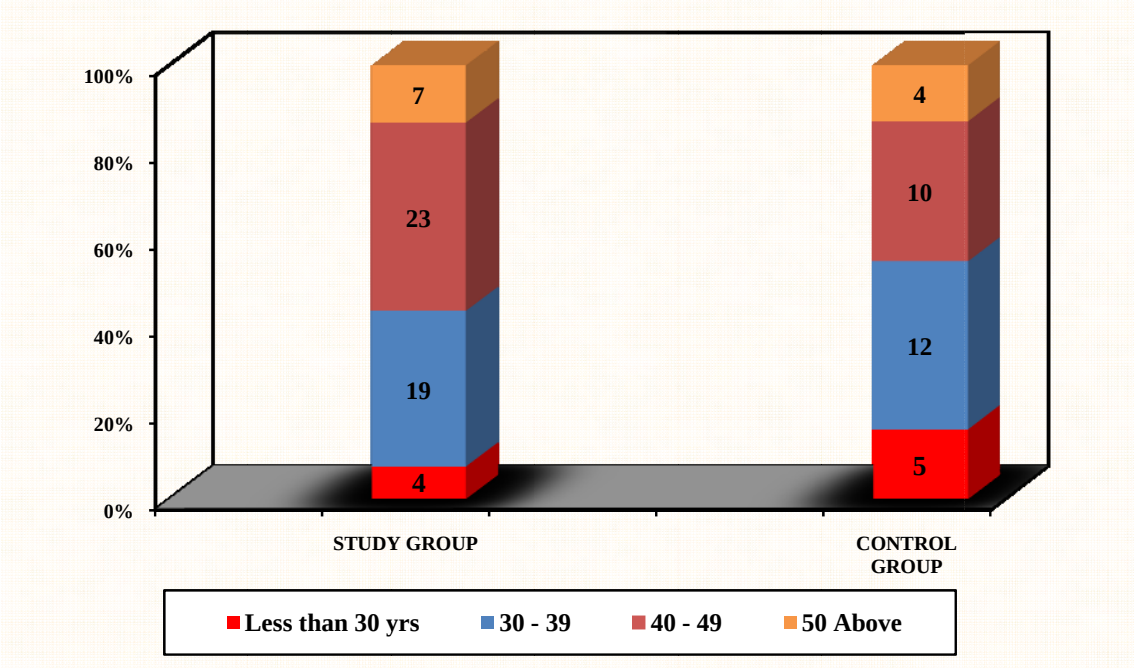
1) BP APPARATUS. **2) STETHESCOPE.**

3) ECG RECORDING. **4) GRIP DYNAMOMETER**

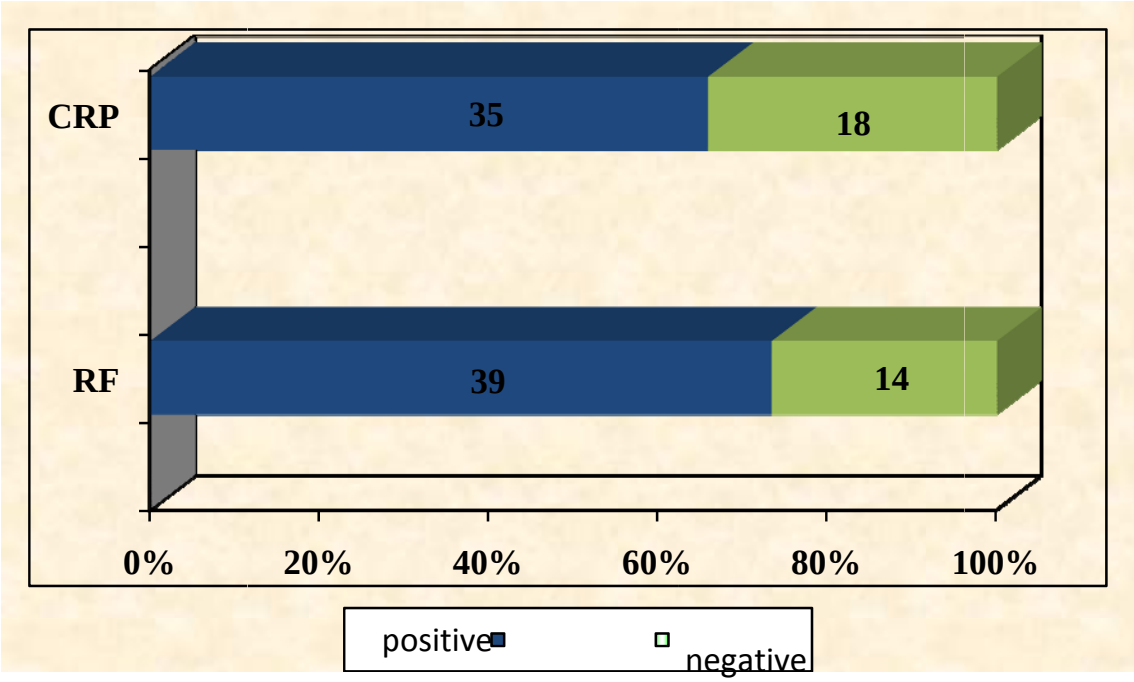
Graph- 1
Sex Distribution among cases and controls



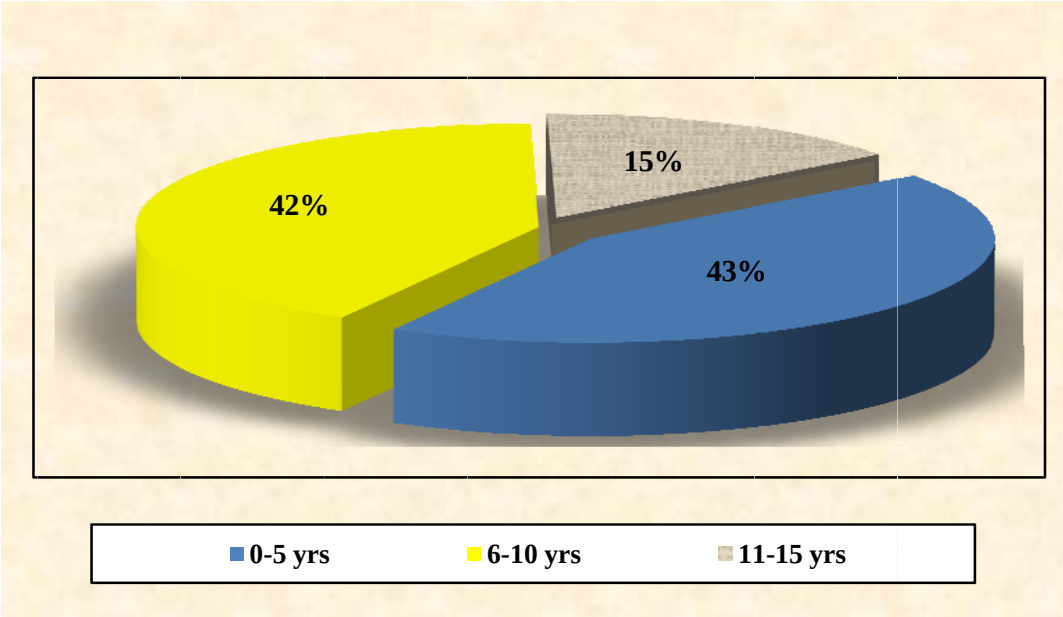
Graph- 2
Age Distribution among cases and controls



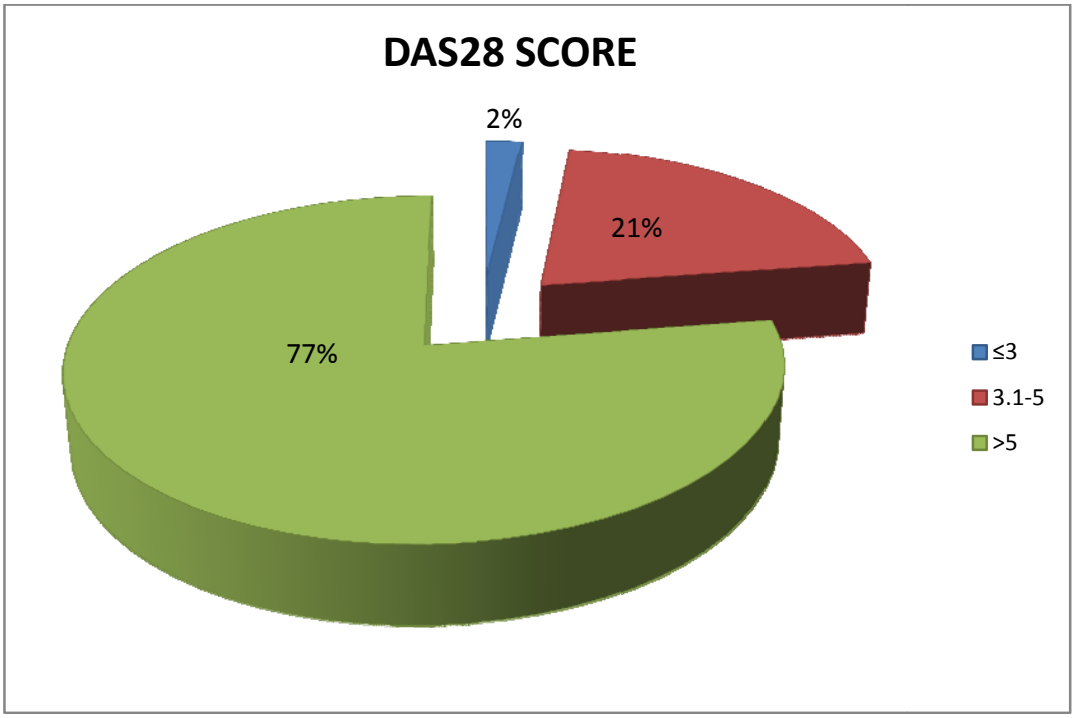
Graph- 3
Qualitative parameters
CRP and RF among cases



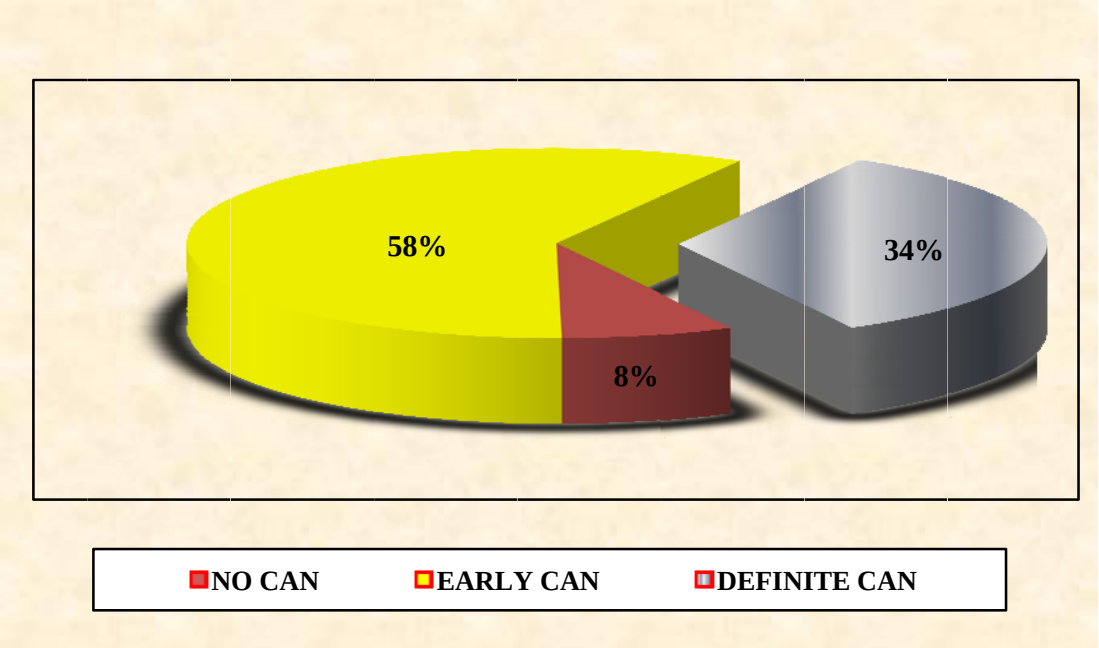
Graph- 4
Qualitative parameters
Disease duration among cases



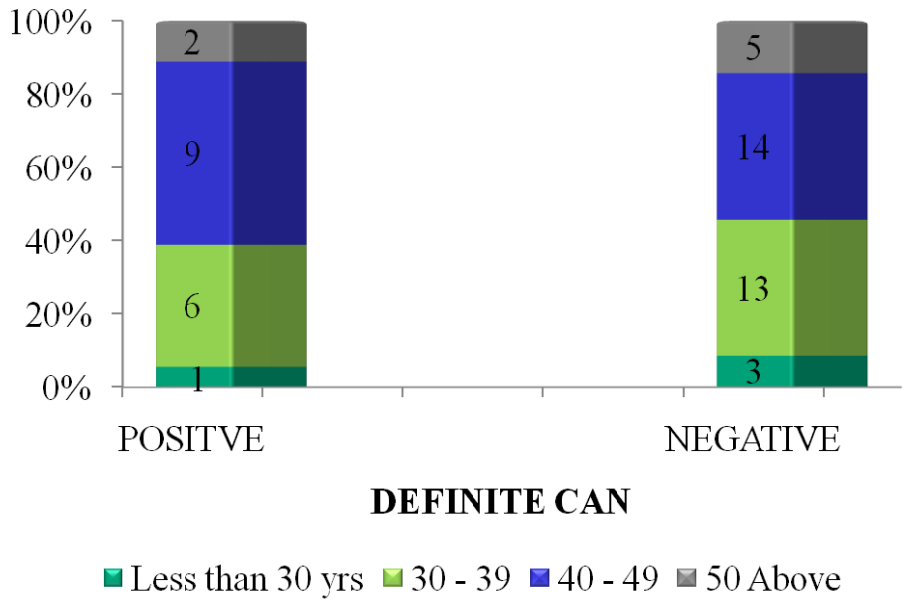
Graph- 5
DAS28 distribution among cases



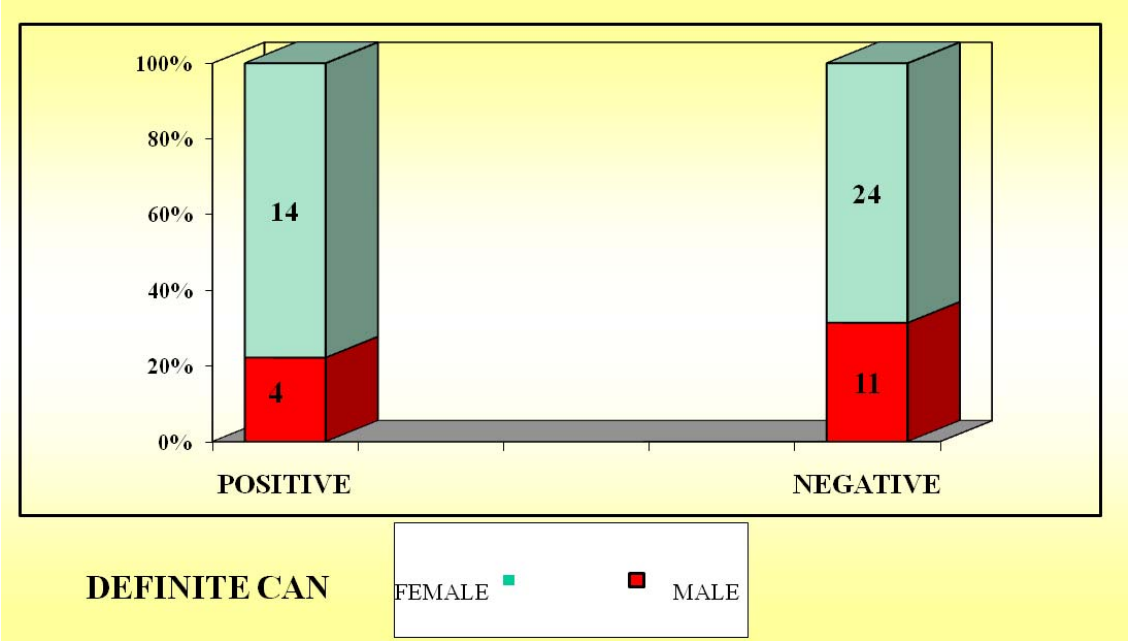
Graph- 6
DAS28 distribution among cases



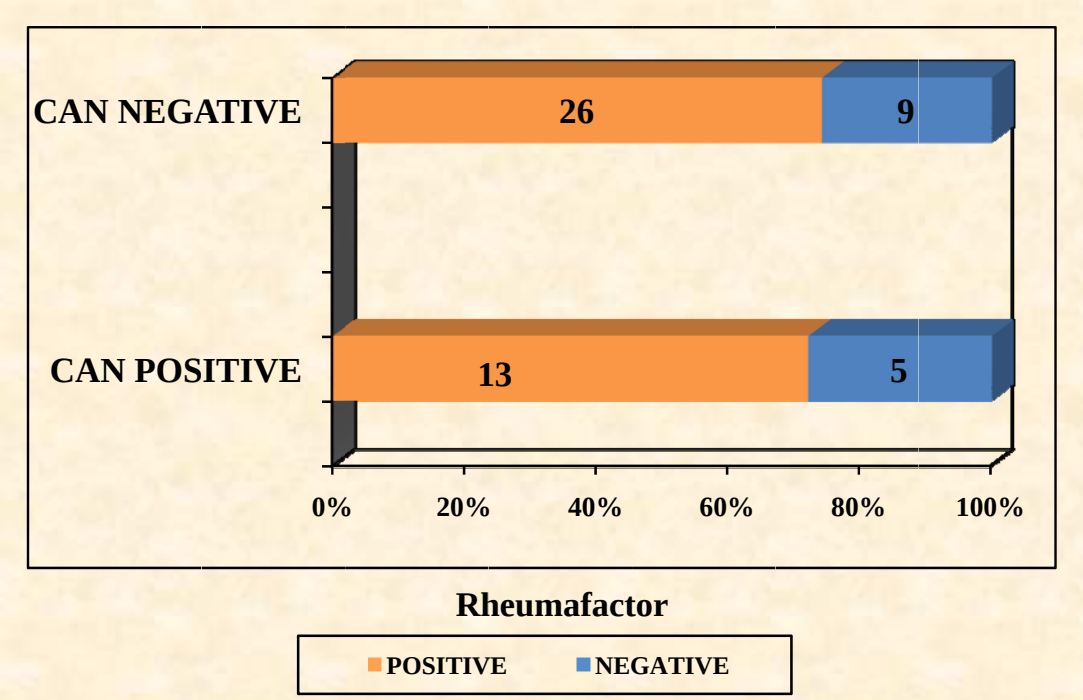
Graph- 7
Definite CAN and Age Comparison



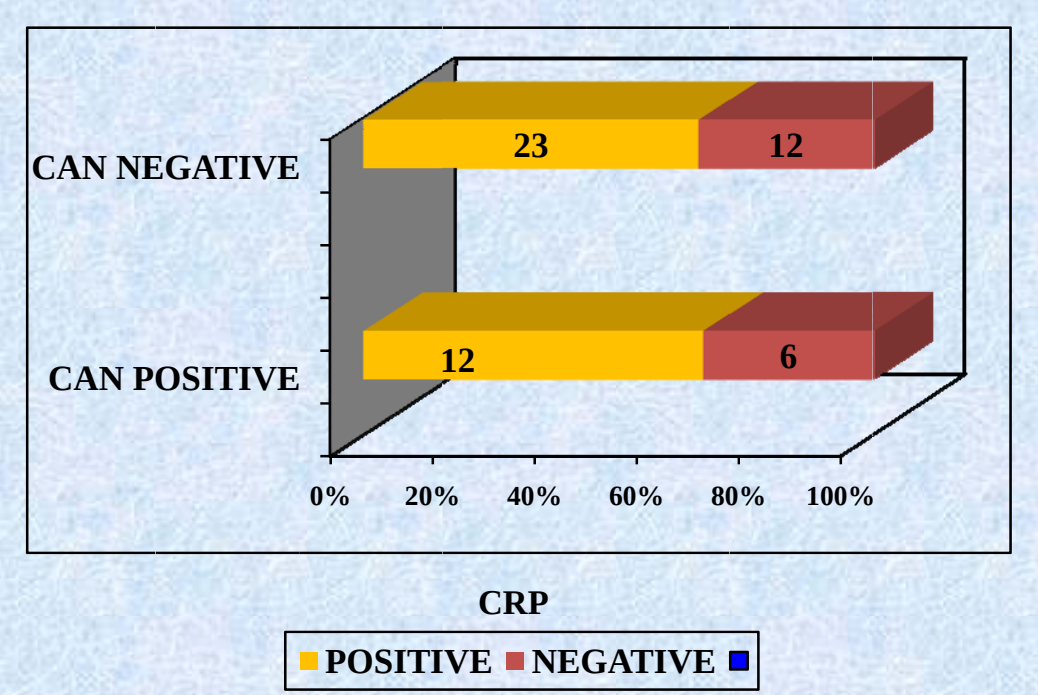
Graph- 8
Definite CAN and Sex Comparison



Graph- 9
Definite CAN and RF Comparison



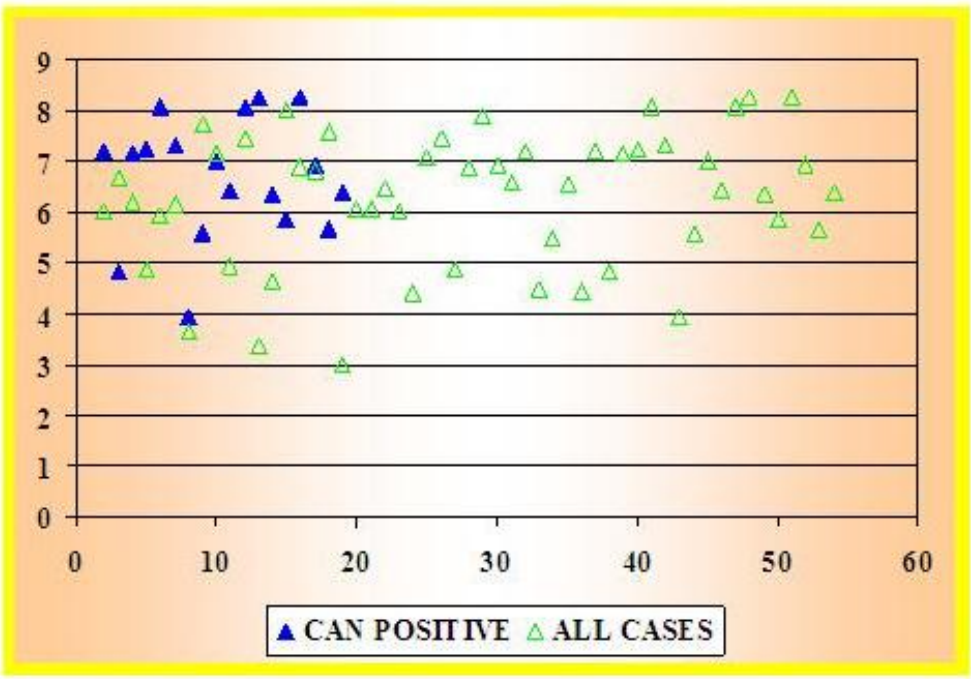
Graph- 10
Definite CAN and CRP Comparison



Graph- 11

Comparison of DAS 28 distribution among

definite CAN patients and cases



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